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Short Communication

Durability of Response with First-Line Combined Immune Checkpoint Inhibitor Therapy Compared to Checkpoint Inhibitor with VEGFR-TKI in Advanced Clear Cell Renal Cell Carcinoma

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Abstract. Over the past several years, four regimens incorporating immune checkpoint inhibitors have become widely used in the front-line setting to treat metastatic clear cell renal cell carcinoma: nivolumab with ipilimumab, axitinib with pembrolizumab, cabozantinib with nivolumab, and lenvatinib with pembrolizumab. These regimens all demonstrated favorable response rates and survival outcomes compared to sunitinib in phase III trials. As these data have matured, nivolumab with ipilimumab has been most clearly associated with durable long-term disease response and stable survival benefit. Moreover, responses obtained using nivolumab with ipilimumab are more likely to persist after treatment discontinuation compared to regimens containing a VEGFR-TKI. These outcomes underline the value of using nivolumab with ipilimumab to pursue durable response in patients with advanced clear cell renal cell carcinoma.

Keywords: Checkpoint inhibitor, metastatic ccRCC

In the immune checkpoint inhibitor (ICI) era, the goal of treatment for many patients with clear cell renal cell carcinoma (ccRCC) and their physicians has shifted from delaying cancer progression to inducing durable tumor regressions with potential for cure. Four regimens incorporating ICIs have been most widely used as front-line treatment for patients with metastatic ccRCC: nivolumab with ipilimumab (nivo/ipi), axitinib with pembrolizumab (axi/pembro), cabozantinib with nivolumab (cabo/nivo), and lenvatinib with pembrolizumab (len/pembro). These regimens were approved by the FDA in the front-line setting and have been widely adopted based on the results of phase III trials demonstrating favorable response rates and survival outcomes. With extended follow-up and analyses of many of these cohorts after com-

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pletion of front-line therapy, a clearer picture has emerged of the relative potential for each regimen to provide durable response and stable survival benefit.

Nivo/ipi was first evaluated in this setting in CheckMate 214 [1]. In the intention-to-treat (ITT) population, treatment with nivo/ipi was associated with an 18-month OS rate of 78% versus 68% in the sunitinib arm, with a hazard ratio (HR) for death of 0.68 (99.8% CI, 0.49–0.95). When stratifying by IMDC risk, this effect was seen in the intermediate- and poor-risk groups, but not for those with favorable-risk disease. However, the IMDC categories were developed in patients receiving anti-vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) and their predictive value for ICI-based therapies has not been established. Nivo/ipi was also associated with objective response rate (ORR) of 39% versus 32% in the sunitinib group. The OS benefit of nivo/ipi has persisted through multiple extended follow-up analyses; most recently, the 90-month OS for nivo/ipi was 35.1% versus 24.9% for sunitinib (HR 0.72, 95% CI, 0.62–0.83) [2]. Of particular note, the median duration of response (DOR) in the nivo/ipi group was 82.8 months (95% CI, 54.1-NE) versus 19.8 months (95% CI, 16.4–26.4) in the sunitinib group (HR 0.48, 95% CI 0.33–0.69).

Results for axi/pembro, cabo/nivo, and len/pembro were reported in subsequent phase III trials [3–5]. These regimens were associated with ORRs of 59.3% with axi/pembro, 55.7% with cabo/nivo, and 71.0% with len/pembro in the ITT populations. In KEYNOTE-426, axi/pembro was associated with an 18-month OS of 82.3% versus 72.1% with sunitinib, (HR 0.53, 95% CI, 0.38–0.74). In CheckMate 9ER, cabo/nivo and sunitinib were associated with 12-month OS rates of 85.7 and 75.6%, respectively (HR 0.60, 98.89% CI, 0.40–0.89). In the CLEAR trial, the 24-month OS rates were 79.2% with len/pembro and 70.4% in the sunitinib group (HR 0.66, 95% CI, 0.49–0.88). Despite these encouraging early efficacy outcomes, extended follow-up analyses of these trials have shown a consistent trend of attenuating OS benefit for the ICI/VEGFR-TKI regimens versus sunitinib (Fig. 1) [6–8]. Further, the median DORs for axi/pembro, cabo/nivo, and len/pembro were 23.6 months (range, 1.4–68.6), 22.0 months (95% CI, 18.0–25.2) and 26.7 months (95% CI, 22.8–34.6), respectively.

The durability of response seen with the ICI-based combinations can be further assessed via partitioned survival analysis, and in particular through evaluation of treatment-free survival (TFS), defined as the area between Kaplan-Meier curves for time from randomization to protocol therapy cessation and for time from randomization to subsequent systemic therapy initiation or death, estimated over a restricted time period [9]. In an analysis of the CheckMate 214 ITT population, nivo/ipi was associated with a 42-month mean TFS of 7.8 months versus 3.3 months for sunitinib [10]. Many of these patients have achieved long-term treatment-free remission and may in fact be cured. A similar assessment over a 30-month period was performed on the pooled populations from KEYNOTE-426, CheckMate 9ER, and JAVELIN Renal 100, a trial which compared axi and avelumab to sunitinib in advanced ccRCC [11–14]. Mean TFS was 2.7 months in the ICI/VEGFR-TKI versus 2.9 months in the sunitinib group [11]. Therefore, nivo/ipi was associated with a more prolonged period of disease control after treatment discontinuation than was seen with either sunitinib or combined ICI/VEGFR-TKI therapy.

Preclinical evidence suggesting that VEGFR-TKIs can enhance an ICI-mediated antitumor effect provided the basis for investigating ICI/VEGFR-TKI combination therapy [15]. However, there are also data suggesting that VEGFR-TKIs may instead diminish tumor immune responses in RCC by inducing tumor hypoxia with downstream infiltration of regulatory T cells and myeloid suppressor cells [16, 17]. Tissue hypoxia has been shown to reduce immune function by many mechanisms [18, 19]. This negative effect of VEGFR-TKI therapy on immune function is most evident clinically in patients with IMDC favorable risk RCC, a group that is enriched for patients with high angiogenesis expression signatures, where OS HRs all exceeded 1.0 for the ICI/VEGFR-TKI combinations relative to sunitinib, while in CheckMate 214 the OS HR has fallen over time to 0.82 for nivo/ipi versus sunitinib in this population [2–5, 20]. Further evidence for a potential antagonistic relationship is provided by the phase III LEAP-003 trial comparing len/pembro versus pembro plus placebo as front-line therapy for metastatic melanoma. In this trial, the len/pembro arm, despite early improvements in ORR and median PFS, had worse DOR and OS compared to pembro plus placebo [21].

In the absence of prospectively randomized trial data, comparisons between nivo/ipi and ICI/VEGFR-TKI are limited by differences in the trial designs,

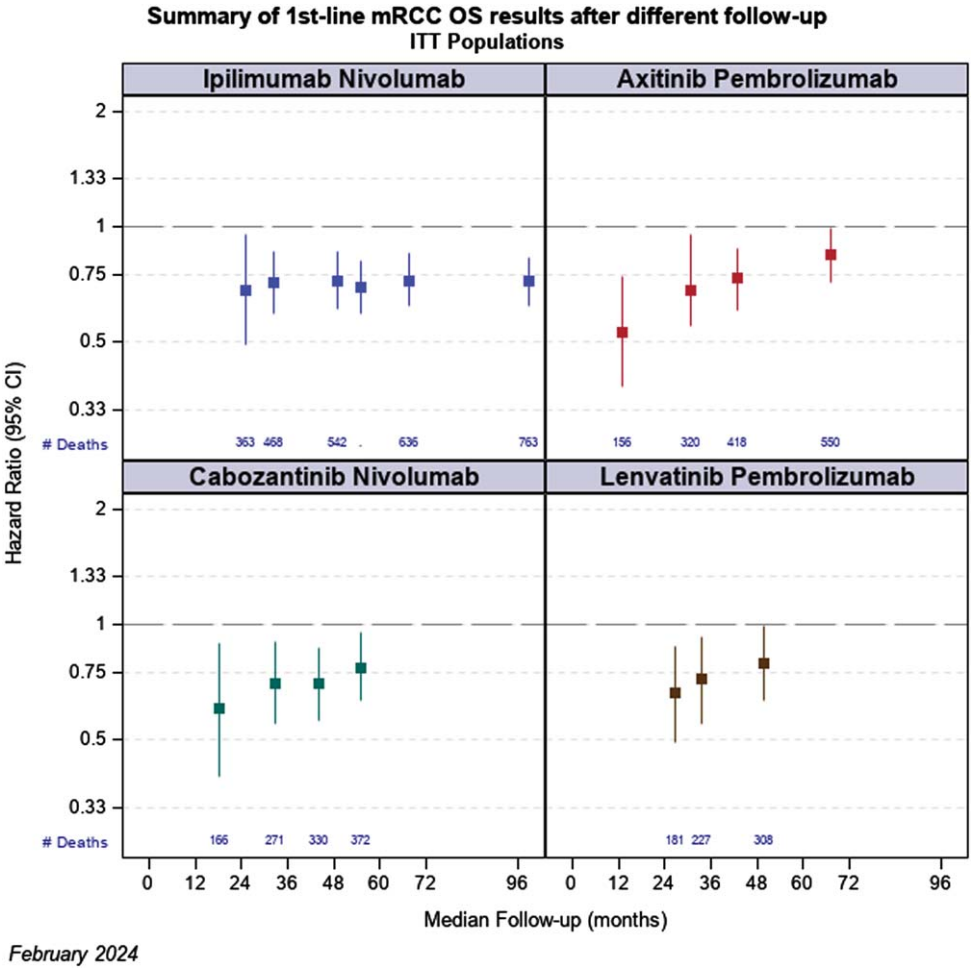

Fig. 1. Summary of 1st-line metastatic ccRCC OS results in the ITT populations after different follow-up periods. Adapted from a figure proposed by Tom Powles [23].

underlying patient populations, study time periods, and availability of subsequent systemic therapies. Despite these limitations, nivo/ipi shows clear evidence of durable response and OS benefit even 7.5 years after initial treatment and after treatment discontinuation, a pattern that has not been demonstrated with the ICI/VEGFR-TKI combinations. In an updated 43-month analysis for KEYNOTE-426 and prespecified 4-year final analysis of the CLEAR trial, it was suggested that the attenuated treatment benefits on OS over time were related to patients in the sunitinib arms receiving ICI salvage therapy following disease progression, as stronger HRs for death were found when adjusting for subsequent anticancer therapy [8, 13]. However, a systematic review of second-line therapies in the control arms of multiple phase III ccRCC trials showed that the sunitinib group in CheckMate 214 received second-line ICI therapy at a rate similar to those in other trials, indicating that this factor cannot fully explain the persistent OS benefit seen with nivo/ipi relative to ICI/VEGFR-TKI [22].

The treatment of advanced ccRCC has fundamentally changed with the advent of ICI therapy. Essential to this shift is the potential for patients to achieve prolonged responses that persist even when treatment is stopped. Of the regimens that have been investigated in this setting, the ICI combination nivo/ipi has most clearly demonstrated benefits that are inkeeping with this goal. The evidence supports the use of nivo/ipi in cases of advanced ccRCC where durable response and remission are being pursued, as well as the use of a pure ICI backbone as the basis for future investigative therapies.

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AUTHOR CONTRIBUTIONS

JZ, DFM, and MBA all contributed to the manuscript conception. JZ, DFM, MR, and MBA all contributed to data interpretation and manuscript writing. MR contributed to figure generation.

CONFLICTS OF INTEREST

Jacob Zaemes has served as a consultant for MJH Life Sciences.

David F. McDermott has received institutional funding from Bristol-Myers Squibb, Merck, Genentech, Novartis, and Alkermes. David F. McDermott has served as a consultant for Bristol-Myers Squibb, Merck, Genentech/Roche, Pfizer, Exelixis, Novartis, Array BioPharma, Peloton, EMD Serono, Jounce Therapeutics, Alkermes, Lilly, Eisai, Calithera Biosciences, Iovance Biotherapeutics, Werewolf Therapeutics, Synthekine, AVEO, Xilio Therapeutics, and Cullinan Oncology.

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DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed during the course of this study.

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